

EIS Clinical Pre-Study of Patients Undergoing Chemotherapy

Clinical Investigator and Monitor

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Summary

Thirty-nine (39) patients undergoing chemotherapy were measured with the EIS (Electro Interstitial Scanner) System at the Gustave Roussy Institute (GRI) in Villejuif, France, with the aim of investigating the effects of their cancer treatment, and in particular their chemotherapy treatment, in terms of interstitial fluid volumes.

The results from this group were compared with EIS results from a control group of 40 healthy subjects.

The EIS System measurements provided:

- An ElectroScanGram (ESG) of the conductivities of 22 interstitial fluid volumes of the human body
- The acid base balance measured in interstitial fluid
- Tissue oxygenation

Hypotheses

The hypotheses of this pre-study were:

1. In reference to the said study database, the ESG graph, the interstitial fluid acid base balance, and the tissue oxygenation measured by the EIS system could offer the possibility of being used as a marker for chemotherapy follow-up.

This hypothesis was validated by the following results:

- After a statistical study of the said database using the statistical method Mean Plot: Whisker using STATISTICA version 6.0, it appeared that the ESG graph presented a level of sensitivity of 95% (IC calculated at 95%) in the patients undergoing chemotherapy compared to the control group, and a level of specificity of 89% (IC calculated at 95%).
- The interstitial fluid of the sampled database had an average pH of 7.41 (control group: 7.33).
- The tissue oxygen was reduced: 67 mm /Hg (control group: 80 mm/Hg).

2. The number of patients for this study is sufficient for the statistical analysis in order to calculate a level of specificity for the ESG graph.

This second hypothesis was validated by the calculation of the specificity. However, for more precision regarding sensitivity, a meta analysis is necessary.

Justification

Cancer and its treatment protocol typically launch a polymorphic and simultaneous attack on the organism in all its compartments. There is no body system, whether chemical, hormonal, nervous, metabolic, or electrophysiological, that can withstand cancer and/or its treatment.

Cancer involves a reduction in tissue oxygen and acid interstitial fluid and also affects mitotic genetic processes, totally disorganizing and exhausting these systems relatively rapidly.

The entire homeostasis of the organism is disrupted. The mechanisms of exchange intra- and extra-cellular find themselves totally destabilized. This has, as a consequence, the progressive alteration of bio conductivities, a reduction of oxygen, pH imbalance, and tissue aggregation.^{(14), (15)}

Since the EIS System was designed to evaluate these parameters, there was an interest in recording the relevant clinical data specific to the cancer treatment, i.e., chemotherapy. An EIS device was therefore placed at the disposal of the GRI in order to carry out this study.

The EIS System

The principle of the EIS System is the measurement of the conductivity of interstitial fluid locally and in vivo using the technique of bioelectrical impedance with specificity via the EIS System, which employs a DC current.^{(17), (18)}

This measurement uses six electrodes:

- Two on the forehead
- One on each hand
- One on each foot

From these six electrodes, 22 tissue volumes are measured and are recorded in a graphic display. The graphic display of the conductivity values of these 22 volumes is called an ElectroScanGram (ESG).

Using the technology of biosensors and application of chronoamperometry (Cottrell equation), the EIS System also makes it possible to calculate interstitial fluid pH and tissue oxygenation.

Tested hypotheses

The questions raised for investigation were:

1. In reference to the said study database, could the ESG graph, the interstitial fluid acid base balance, and the tissue oxygenation provided by the EIS System offer the possibility of a marker for chemotherapy follow-up?
2. Would the number of patients in this study be sufficient for statistical analysis in order to calculate a level of specificity for the ESG graphic?

STUDY CONDITIONS

Site of investigation

The recordings took place at the Centre for Research and Treatment of Pain for Children and Adults at the Gustave Roussy Institute, Villejuif, France.

Agreement of the GRI Scientific Committee

Dr. David Alimi (Research and Consultations at the GRI) developed the protocol for this clinical research.

Following a medical conference, he spoke to interested colleagues about the scientific bases and principles of the EIS System and its total safety for both personnel and patients. He obtained the agreement of the Scientific Committee to use the system at the GRI on the formal condition that there would be no interference with any patient's current or future treatments.

He received an EIS device from the manufacturer for this study during a period of nine months beginning in May 2002.

Subjects excluded

Excluded from testing were patients who:

- Had skin lesions in contact with the electrodes or excessive perspiration
- Had been fitted with pacemakers
- Were unable to be seated
- Had been fitted with metal pins or prostheses in the lower limbs or joints
- Were pregnant women after the sixth month
- Were missing one or more limbs
- Used therapeutic pumps
- Were one month or less post-surgery
- Refused to sign the enlightened consent form
- Had mental and/or behavioral problems that kept them from understanding the enlightened consent form

Patients recruited

Two groups of patients were established:

- **Group 1:** A control group of 40 subjects in supposed good health. This group was recruited from GRI employees and their families. These subjects had no pathology, were not undertaking cancer treatments, and were not taking medications.
- **Group 2:** These patients were subjects in consultation at the GRI for pain post treatment for cancer.

The patients in Group 2 were addressed either by their practitioner or by other medical and surgical department staff. All their treated pathologies were oncological in nature, either benign or malignant.

All types of cancerous localizations, primitive and secondary, were present in the registered patients. Their pathologies were of various types, including epithelial (carcinoma), mesodermal (sarcomas), cutaneous (epithelioma), or visceral (deep cancers).

Recording took place as often as possible in the clinical environment during consultations, with care taken not to disturb daily hospital routines. All patients had chemotherapy treatment (eventually accompanied by surgery and/or radiation) for a period of one month to four years. All the patients were seen for post-treatment pain (neuropathy).

Period of study and number of patients

Registrations were accepted from May 2002 to January 2003. Forty subjects participated in Group 1 (17 male and 23 female) and 39 patients (12 male and 27 female) participated in Group 2 of this study.

Enlightened consent

After the safety aspects and all parameters of the study were presented to the patients, their free and informed consent was obtained and they signed an enlightened consent form.

Monitoring

Dr. David Alimi personally carried out all recording during his consultation hours at the GRI.

Confidentiality

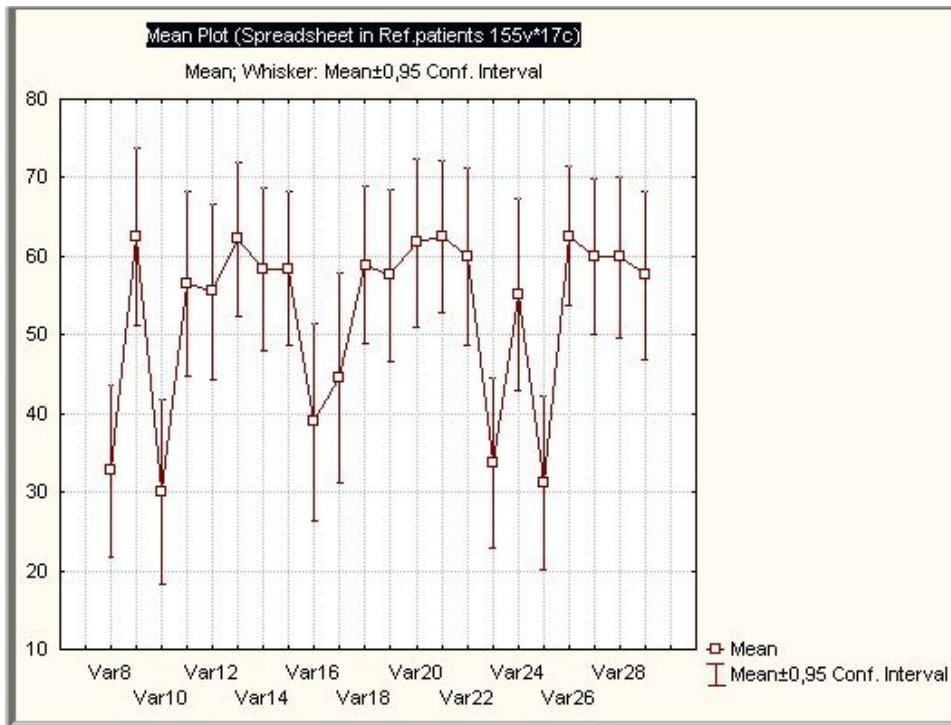
Due to patient confidentiality, identities of all the patients were kept anonymous and each patient was numbered by date of examination. Only clinical and therapeutic data were mentioned for each patient.

RESULTS

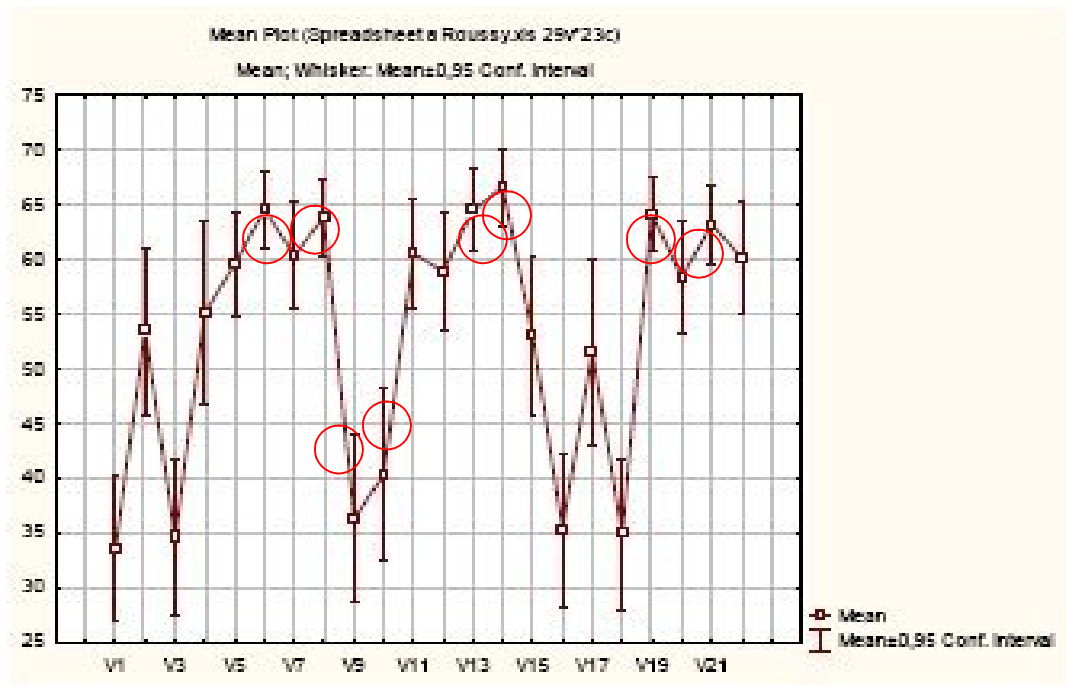
Statistical results are under the responsibility of the sponsor and issue from biostatistics of the patients' database.

See below the statistical analysis of the ESG graph carried out with the method Mean Plot: Whisker (program STATISTICA, version 6.0).

This graph represents the average of the ESG graph for the two group databases.



Group 1: Control group



Group 2: Chemotherapy patients

The results of this graph and the reference graph determine a sensitivity of 95% and a specificity of 89% (IC calculated to 95%).

Volumes 6/8/13/14/19/21: Group 2 > Group 1

Volumes 9/10: Group 1 < Group 2

The calculation of acid base balance realized by the system on the entire database showed an average for the interstitial fluid pH (ipH) of about 7.41. The norms of the interstitial fluid pH being 7.33, the patients in Group 2 presented a significant metabolic alkalosis, undoubtedly due to the cytotoxic chemotherapy treatment.

The calculation of tissue oxygenation (tO₂) on the database showed an average of about 67 mm/Hg. The norms of tO₂ being 80mm/Hg, the patients in Group 2 presented a significant hypoxia, undoubtedly due to the cytotoxic chemotherapy treatment, which helped to explain post-treatment pain.

CONCLUSIONS

These conclusions involve only the sponsor of this pre-study.

The EIS System, according to the results obtained by the statistical method used, should be a marker for patients undergoing chemotherapy treatment.

This marker specificity is based upon the ESG graph but also on the data re interstitial fluid alkalosis and hypoxia after chemotherapy treatment. Hypothesis 1 is validated.

The number of patients (39) seems sufficient to determine specificity and sensitivity. Hypothesis 2 is also validated.

However, a future meta analysis with the recording of more pathologies will determine with more precision the sensitivity of obtained results.

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